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Melanoma, thyroid, cervical, and colon cancer risk after use of fertility drugs

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Objective: This study was undertaken to evaluate melanoma, thyroid, colon, and cervical cancer risks after clomiphene or gonadotropins.

Study design: Retrospective cohort of 8422 women (155,527 women-years) evaluated for infertility (1965-1988). Through 1999, cancers were ascertained by questionnaire, cancer and death registries. Poisson regression estimated adjusted rate ratios (RRs).

Results: Clomiphene use did not significantly increase risk of melanoma (RR = 1.66; 95% CI, 0.9-3.1), thyroid (RR = 1.42; 95% CI, 0.5-3.7), cervical (RR = 1.61; 95% CI, 0.5-4.7), or colon cancer (RR = 0.83; 95% CI, 0.4-1.9). We found no relationship between clomiphene dose or cycles of use and cancer risk at any site. Clomiphene use may impart stronger effects on risks of melanoma (RR = 2.00; 95% CI, 0.9-4.6) and thyroid cancer among women who remained nulliparous (RR = 4.23; 95% CI, 1.0-17.1). Gonadotropins did not increase cancer risk for these sites.

Conclusion: Fertility drugs do not appear to have strong effects on these cancers. Nonetheless, follow-up should be pursued to assess long-term risks and to monitor effects among women who remain nulliparous.

Cumulative exposure to reproductive hormones has been shown to increase risk of hormone-sensitive carcinomas, particularly those of the endometrium, breast, and ovary that have distinct age-specific rate patterns that are attenuated after menopause.[1,2] We recently reported that clomiphene citrate increases uterine cancer risk in a dose-response and time-dependent manner,[3] and that fertility drug use may also be associated with slight increases in breast and ovarian tumors after long latency periods.[4,5]

Links between hormonal factors and melanoma,[6] colon cancer,[7] thyroid cancer,[8] and cervical cancer,[9] although considerably weaker, have also been suggested based primarily on purported associations with parity or exogenous hormone usage. Few reports have assessed

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the risk of these cancers associated with fertility treatments among infertile women, with small numbers of cancers and inconsistent results.[10-13] This report summarizes melanoma, thyroid, cervical, and colon cancer risk among a large cohort of women from different clinical sites in the United States. Strengths of the study included nearly 20 years of average follow-up and information on other predictors of cancer risk, including specific causes of infertility and reproductive status through follow-up.

Materials and methods

Brinton et al[5] previously described this retrospective cohort study, which was conducted at 5 large reproductive endocrinology practices in the following metropolitan areas: Boston, Mass; New York City, NY; Chicago, Ill; Detroit, Mich; and the San Francisco Bay Area, Calif. The institutional review boards at the collaborating centers as well as at the National Cancer Institute (NCI) approved the study protocol. Briefly, eligible patients were evaluated for infertility between 1965 and 1988 at participating centers where they were seen more than once, or if seen only once, were referred by another physician who provided substantive medical information. Patients with either primary or secondary infertility (nulligravid and gravid, respectively) were eligible for the study, whereas those who were evaluated for reversal of a tubal ligation were not. Medical records for 12,193 eligible women were abstracted for information pertaining to all procedures and tests (allowing a determination of different causes of infertility), medications prescribed (including clomiphene citrate and a variety of human gonadotropins, namely, Pergonal, Humegon, or Metrodin), menstrual and reproductive histories, and other factors that might affect health status.

A total of 9751 (80.0%) of the patients were successfully traced with the use of several sources, including clinic records, telephone directories, credit bureaus, postmasters, motor vehicle administration records, and the National Death Index. A total of 1319 of the eligible women (10.8%) indicated on contact that they did not want to participate in the study. For these women, we retained only information on calendar year and age at study entry, and race.

For the patients traced as alive (we identified 272 patients as deceased), clinic records, completed questionnaires, and cancer registries provided information on the development of cancers. We mailed questionnaires to patients beginning in 1998, with telephone follow-up attempted for nonrespondents. A total of 5597 of the patients completed the questionnaire that ascertained information on sociodemographic factors, updated health status, and lifestyle factors, including menstrual, pregnancy, and breastfeeding history; use of exogenous hormones; and anthropometric factors. For patients for whom we were unable to obtain questionnaire data, we had accurate location information on cancer status through clinic records (216), or cancer registries (2347) if the women last resided in California, Florida, Illinois, Massachusetts, Minnesota, New Jersey, New York, and Texas (eg, the states in which the majority of patients were last known to reside). We attempted to medically verify cancers reported in the questionnaires by obtaining discharge summaries, operative reports, and pathology reports from the institutions where the diseases had been diagnosed and/or treated. Eleven of the self-reported melanomas and 1 colon cancer were found on medical record review to be benign and were excluded from analytic consideration.

Statistical methods

Person-years accrual began 1 year after clinic registration and continued through the earliest date of cancer diagnosis, death, or date last known alive and free of cancer (as indicated by the last clinic visit, questionnaire completion, or linkage against cancer registry data). Patients having cancer registry searches had variable study ending dates, depending on the completeness of registration, which ranged from the end of 1997 to 1999. Otherwise, December 31, 1999, defined the end of the study period. Patients lost to follow-up after their initial clinic visit, those who denied access to their records, and 10 woman who had cancer diagnosed within 1 year of their registration clinic visit were excluded, leaving 8,422 analytic study subjects and 155,527 person-years (mean = 18.8 years) of follow-up.

We used 2 analytic approaches to assess cancer risk among the cohort members. We first calculated standardized incidence ratios (SIRs) and 95% CI comparing cancer rates of infertile women with those of US women. SIRs were computed as the number of observed cancer events divided by the expected number of events that were based on age, race, and calendar year-specific incidence disease rates for women from cancer registry rates available through the Surveillance Epidemiology and End Results (SEER) Program of the NCI. The SEER program has population-based catchment areas and is widely used to estimate cancer burden in the United States.

The second analytic approach involved analyses within the cohort of infertile women, which allowed multivariate adjustment for potential confounding factors. Rate ratios (RRs) and their 95% CIs for developing cancer associated with administration of ovulation-stimulating drugs (ever use, total dosage, cycles prescribed, interval since first use) as compared with nonusers were estimated by Poisson regression with the use of standard methods.[14] For all analyses, the RRs were adjusted for study site, age at follow-up (<40, 40-49, 50+), and

Table I Standardized incidence ratios comparing cancer risk among infertile women to the general population

	Observed	Expected	SIR	95% CI
All sites, excluding nonmelanotic skin	581	473.8	1.23	1.1-1.3
Hormone-sensitive cancers				
Uterine corpus	39	24.9	1.57	1.1-2.1
Breast	292	226.5	1.29	1.2-1.4
Ovary	45	22.7	1.98	1.4-2.7
Postulated hormone-sensitive cancers				
Colon	28	15.9	1.76	1.2-2.6
Melanoma	42	26.7	1.57	1.1-2.1
Thyroid	18	18.1	0.99	0.6-1.6
Cervical	14	23.0	0.61	0.3-1.0

SIRs were computed as the number of observed cancer events divided by the expected number of events based on age, race, and calendar year-specific incidence disease rates for women from cancer registry rates available through the SEER Program.

calendar year of follow-up (before 1980, 1980-1989, 1990, or later), and gravidity at entry. Factors that were available from the medical records, such as cause of infertility, smoking history, and body mass at entry, were included in the regression models, as necessary, to evaluate their roles as potential confounding or modifying factors. For the subjects who completed the questionnaire, we evaluated additional predictors of risk, such as parity and gravidity at follow-up and hormone replacement use.

Results

Description of subjects included in analysis

The median year of first evaluation was 1978 and the median age of the study subjects at first evaluation was 30 years. Nearly 80% of the subjects were known to be white and 43% were evaluated for primary infertility. A total of 3276 (39%) of the study subjects were prescribed clomiphene to treat their infertility, whereas 865 (10%) received gonadotropins. Subjects included in the analyses and those excluded were not significantly different according to calendar year and age at first evaluation; however, a larger proportion of the subjects excluded from analysis had missing information on race (30% vs 11%).[5]

SIRs analysis of cancer

Infertile study subjects developed cancers at higher rates than women in the general SEER population (SIR = 1.23; 95% CI, 1.1-1.3) (Table I). Elevation in risk was evident for tumors that are most well-recognized as having hormonal causes, namely, cancers of the uterine corpus (SIR = 1.57), breast (SIR = 1.29), and ovary (SIR = 1.98), as well as colon cancer (SIR = 1.76) and melanoma (SIR = 1.57). Thyroid (SIR = 0.99) and cervical cancer risk (SIR = 0.61) were the only malignancies postulated to have a hormonal cause that were not more frequently diagnosed among infertile women in the study cohort compared with the general population. Infertile women did not have a higher risk of cancers at other sites, when assessed individually or in aggregate (data not shown).[15]

Clomiphene-exposed women were at higher risk of tumors at only 2 sites: uterus (SIR = 2.14; 95% CI, 1.3-3.3 discussed in detail in Althuis et al[3]) and melanoma (SIR = 2.00; 95% CI, 1.3-3.1). Risk among women not exposed to clomiphene was similar to the general population for both of these cancer sites, with SIRs of 1.25 (0.8-1.9) and 1.28 (0.8-2.0), respectively. We found no difference in risk among "ever used" compared with "never used" clomiphene users for the remaining cancer sites. In addition, cancer risk did not vary by gonadotropin use when comparing cohort members were compared with the US population (data not shown).

Internal analyses of cancer risk

To assess the influence of ovulation-stimulating drugs on cancer risk while adjusting for other predictors of cancer risk (including gravidity), subsequent analyses were within the population of infertile women, comparing drug users with nonusers. We found little evidence to suggest that melanoma, thyroid, cervical, or colon cancer risk was increased by ovulation-stimulating drugs within the cohort of infertile women (Table II). Although point estimates for melanoma (RR = 1.66; 95% CI, 0.9-3.1), thyroid cancer (RR = 1.42; 95% CI, 0.5-3.7), and cervical cancer risk (RR = 1.61; 95% CI, 0.5-4.7) were modestly elevated among clomiphene users, these findings were not statistically significant and there was no dose-response with more detailed parameters of drug usage (dosage and cycles) for any site. Clomiphene use appeared to impart stronger effects on risks of melanoma, thyroid, and cervical cancer among women who were followed for 15 or more years, with RRs relative to never users of 2.08 (0.9-4.9), 1.54 (0.3-8.0), and 2.67 (0.6-11.9), respectively. However, these findings were based on small numbers and did not reach statistical significance. Risk associated with ever compared with never clomiphene use was 0.83 for colon cancer, with no increase with dose, cycles of use, or latency. The models for these data were stable, with little difference in risk estimates after adjustment for potential confounding factors or when we restricted our outcomes to medically validated cases (that is, 11 melanoma [high proportion were based on self-report], 13 thyroid, 6 cervical, and 24 colon cancers).

Although limited by small numbers of events, we assessed if the relationship between clomiphene use and cancers varied according to other predictors of cancer

Table II Ovulation stimulating drug use and cancer risk among infertile women

	Melanoma (n = 42)			Thyroid (n = 18)			Cervical (n = 14)			Colon* (n = 28)		
Infertility treatment	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
Clomiphene												
Never	21	1.00		10	1.00		7	1.00		20	1.00	
Ever	21	1.66	0.9-3.1	8	1.42	0.5-3.7	7	1.61	0.5-4.7	8	0.83	0.4-1.9
Dosage (mg)												
1-900	8	1.78	0.8-4.1	5	2.48	0.8-7.4	3	1.85	0.5-7.4	2	0.56	0.1-2.4
901-2250	9	2.23	10.-5.0	1	0.55	0.1-4.4	2	1.42	0.3-7.0	4	1.22	0.4-3.6
>2250	4	0.95	0.3-2.9	2	1.07	0.2-5.1	2	1.48	0.3-7.6	2	0.73	0.2-3.2
Cycles												
<6	16	1.88	0.9-3.7	8	2.14	0.8-5.6	5	1.68	0.5-5.4	5	0.74	0.3-2.0
6+	5	1.20	0.4-3.3	0	—		2	1.43	0.3-7.3	3	1.04	3.0-3.6
Year since first use												
<15	11	1.48	0.7-3.2	6	1.55	0.5-4.4	4	1.37	0.4-5.0	4	0.82	0.3-2.5
15+	9	2.08	0.9-4.9	2	1.54	0.3-8.0	3	2.67	0.6-11.9	4	0.98	0.3-3.0
Missing	1											
Gonadotropins												
Never	38	1.00		16	1.00		12	1.00		28		
Ever	4	0.90	0.3-2.6	2	1.10	0.2-4.9	2	1.39	0.3-6.4	0		

All models adjusted for attained age, calendar time, study sites, and gravidity at entry. Estimates of risk associated with clomiphene were also adjusted for anovulatory disorders, a primary indication for use. Additional adjustment for other causes of infertility did not appreciably change risk estimates.

* Additionally adjusted for body mass index at study entry (quartiles, kg/m^2).

risk (Table III). Melanoma (RR = 1.72), thyroid cancer (RR = 1.83), and cervical cancer risk (RR = 2.89) associated with clomiphene usage was highest among women who were nulligravid at entry when compared with unexposed gravid women. For melanoma (RR = 2.00) and thyroid cancers (RR = 4.23), risk was also elevated among women who remained nulliparous at follow-up, with no elevation among parous women. Cervical cancer risk associated with clomiphene use was not modified by parity at follow-up. Interpretation of these findings is complicated by small numbers of cancer and missing information on parity at follow-up that was available primarily from women who completed the questionnaire. Colon cancer risk associated with clomiphene usage was not modified by either gravidity at entry or parity at follow-up. In addition, the relationship between clomiphene use and cancer risk at these 4 sites was not significantly modified by specific causes of infertility (such as anovulatory disorders or endometriosis) or attained age (data not shown).

Analysis of the relationship between gonadotropins and cancer risk was limited by the small number of exposed women (Table II). Fewer than 5 cases at each site were exposed to gonadotropins, with no apparent elevation in cancer risk.

Comment

Infertile women, as shown in this study and other cohort investigations,[16-19] are at higher risk of cancer than women from the general population. Whether excess cancers diagnosed among infertile women are attributable to underlying causes of infertility, to the women's low parity, or to fertility drugs has been unclear. We previously reported the possible association of fertility treatment with hormone sensitive cancers of the breast, ovary, and uterus in this cohort.[3-5] This report examines risks related to melanoma, thyroid, cervical, and colon cancers, which have been suggested as having possible hormonal causes. Consistent with previous investigations,[11-13,16-23] infertile women in our study were at elevated risk of melanoma (SIR = 1.57) and colon cancer (SIR = 1.76), but not thyroid (SIR = 0.99) or cervical cancer (SIR = 0.61).

In addition to comparisons with the general population, we were able to make comparisons within the population of infertile patients, allowing us to attempt to disentangle the effects of fertility drugs with other predictors of cancer risk, such as parity and specific causes of infertility. It is reassuring that we found little evidence to suggest an association between ovulation-stimulating drug use and cancer risk, and that our findings changed little after adjustment for potential confounding factors such as reproductive and smoking history, cause of infertility, or body mass. There was no significant association overall or with increasing drug use for melanoma (RR = 1.60, based on 21 exposed cases), thyroid (RR = 1.42, based on 8 exposed cases), cervical (RR = 1.61, based on 7 exposed cases), or colon cancer (RR = 0.83, based on 8 exposed cancers). We do, however, present some evidence suggesting that melanoma, thyroid, and cervical cancer risk may increase

Table III Modification of cancer risk associated with ever compared with never clomiphene use by reproductive status

	Melanoma (n = 42)			Thyroid cancer (n = 18)			Cervical cancer (n = 14)			Colon cancer (n = 28)		
	Cancers	RR	95% CI	Cancers	RR	95% CI	Cancers	RR	95% CI	Cancers	RR	95% CI
Gravidity at entry												
Gravid												
No clomiphene	13	1.00		5	1.00		3	1.00		12	1.00	
Clomiphene	12	1.49	0.7-3.3	4	1.20	0.3-4.5	3	1.42	0.3-7.1	4	0.55	0.2-1.7
Nulligravid												
No clomiphene	8	0.78	0.3-1.9	5	1.26	0.4-4.4	4	1.63	0.4-7.3	8	0.84	0.3-2.1
Clomiphene	9	1.72	0.7-4.1	4	1.83	0.5-6.9	4	2.89	0.6-13.1	4	0.83	0.3-2.6
Parity at follow-up												
Parous												
No clomiphene	18	1.00		4	1.00		4	1.00		7	1.00	
Clomiphene	11	0.96	0.5-2.1	2	0.73	0.1-4.0	4	1.43	0.4-5.8	4	0.94	0.3-3.2
Nulliparous												
No clomiphene	3	0.45	0.1-1.5	2	1.35	0.2-7.4	1	0.42	0.1-4.2	2	0.76	0.2-3.6
Clomiphene	8	2.00	0.9-4.6	4	4.23	1.0-17.1	2	1.31	0.2-8.2	3	1.95	0.5-7.6
Parity missing	2			6			3			12		

Models estimated cancer risk associated with ever compared with never clomiphene use adjusted for attained age, calendar time, and study site.

with time because clomiphene usage with RRs of 2.08 (0.9-4.9), 1.54 (0.3-8.0), and 2.67 (0.6-11.9), respectively, among women followed for 15 years or more. These hints of a possible latency effect may suggest that clomiphene is an initiator of carcinogenesis and is consistent with the fact that carcinogenesis is a long process, which takes many years. Accrual of more cancer events via continued follow-up of this and other infertile cohorts is necessary for clarification.

We also found that clomiphene use appeared to impart stronger effects on the risks of melanoma (RR = 2.00) and thyroid cancer (RR = 4.23) among women whom remained nulliparous through follow-up, a finding that is based on few cancers and that also requires confirmation. Clomiphene-associated cancer risk among nulliparous women persisted after adjustment for underlying causes of infertility such as anovulatory disorders, which have been associated with melanoma,[12,15] and endometriosis, which has been associated with melanoma, thyroid, and colon cancers.[15] We cannot entirely exclude the possibility that women who remained nulliparous and who used clomiphene had more severe underlying disease for which we were unable to account.

Early studies linking parity, oral contraceptives, and postmenopausal hormone therapy to melanoma postulated a hormonal cause for this cancer.[24] A relationship between ovulation-stimulating drugs and melanoma was first suggested by case reports[25,26] and by elevations in melanoma risk seen among cohorts of infertile women.[11,12,16,17,23] For the latter, too few cancers have been diagnosed to disentangle the effects of infertility medications from their indications for usage. Of the larger investigations, a cohort study in Seattle found no elevation in melanoma risk overall, but risk was elevated among women who had used clomiphene for 12 or more menstrual cycles (RR = 2.2; 95% CI, 0.5-10.2, based on 4 exposed cases, 3 of whom had ovulatory abnormalities).[23] Consistent with our results, 2 other prior studies that evaluated the relationship between ovulation-stimulating agents and melanoma found no increase in cancer risk,[23,27] although only 1 (a case-cohort design) was able to examine the effect of specific fertility drugs.[27]

Thyroid cancer has been postulated to have a hormonal cause because it is 3 times more frequent in women than men and because risk has been linked to oral contraceptive use[10] and reproductive factors, particularly among those diagnosed at young ages.[8] To date, little evidence of an association between ovulation-stimulating agents and thyroid cancer risk has emerged. A pooled-analysis of case-control studies reported a nonsignificant increased risk of thyroid cancer after infertility drug use (odd ratio [OR] = 1.6; 95% CI, 0.9-2.9),[10] although 1 of the included studies reported a significant 4-fold excess risk.[28] Unlike the case-control design that relies on patient reports of complex infertility treatment, the cohort design enables obtaining information directly from medical records. This allows for more detailed assessment of specific agents and doses. Cohort studies before ours have not evaluated thyroid cancer risk after use of ovulation-stimulating agents because of the few cancers diagnosed.

Although cervical cancer is not generally viewed as a hormonally-related tumor, relationships of the disease with increasing parity and long duration of oral contraceptive use[9] have raised concerns regarding effects of other hormonal agents. The most informative data derive from a retrospective cohort study by Rossing et al conducted in Seattle in which 36 in situ and invasive cervical cancers were detected.[13] In the current study,

which is in line with other studies that have shown that parity is a risk factor for this cancer,[9] infertile women were at a decreased risk of having cervical cancer develop compared with the general population. Contrary to the study by Rossing et al, which reported a reduction in cervical cancer risk associated with clomiphene (RR = 0.4), we found the risk among women who had taken clomiphene was elevated relative to nonusers (RR = 1.61; 95% CI, 0.5-4.7). Neither our study nor the study by Rossing et al reported any apparent relation according to dose or duration of use. It remains unclear as to whether clomiphene may act predominately as an estrogen agonist or antagonist on the cervix.

Hormonal factors have been inconsistently associated with colon cancer risk in women, with some studies showing an inverse relationship with parity and hormone replacement therapy.[7,29] Colon cancer risk associated with infertility and its treatment has received little attention with only 1 other published study, which reported results similar to ours. Specifically, in an Australian cohort of infertile women, 1 colon cancer was diagnosed among women exposed to in vitro fertilization compared with 3 cases among unexposed women.[23]

Whether fertility drugs other than clomiphene increase cancer risk requires further investigation. We previously have reported a non-significant elevation in breast cancer risk among women who used gonadotropins for 6 or more menstrual cycles (RR = 1.50) and who were first exposed 20 or more years ago (RR = 1.54).[4] Melanoma, thyroid, cervical, and colon cancer sites had fewer than 5 exposed cancers and did not show an increased cancer risk with gonadotropin use (RRs from 0.9-1.39).

Although our study had a number of strengths, there were some notable limitations. Although larger than previously published studies, the total number of cancers for each site was small. Given the retrospective nature of the study, we were unable to locate 20% of the study population and 11% did not agree to release their medical records. In addition, 41% of located subjects did not complete a questionnaire, potentially leading to a variety of selection biases that may have affected our results. However, we were unable to detect any systematic selection biases in the current or previous analyses of data from this cohort.[3-5] Information on ovulation-stimulating drugs, although more complete than in most studies, was still less than optimal. Even though information about later drug use was obtained via questionnaire, we could not account for drugs subsequently prescribed by other providers among women who did not complete the questionnaire. Finally, the pattern and dose of drug exposures for many women that we evaluated were quite different from those in current use.

In summary, after accounting for independent contributions of causes of infertility and reproductive status, findings from this study do not suggest an association between ovulation-stimulating drug use and melanoma, thyroid, cervical, or colon cancers. Nonetheless, because clomiphene is one of the most widely used drugs in the management of infertility,[30] extended follow-up of infertile patients is necessary to accrue more cancer events and to clarify the relationship between clomiphene citrate and cancer risk, particularly among infertile women who remain nulliparous.

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